Summary

An example of acute porphyria occurring in a young man is described. Abdominal and mental symptoms and neurological signs were present. Pigmentation and photosensitivity were conspicuous features. There was some evidence of a familial distribution of the disease.

I am indebted to Dr. G. H. Jennings for his encouragement and permission to publish this report; to Prof. C. Rimington for his kindness in performing the assays; to the R.A.M.C. officers whose notes furnished the basis of the early part of the case history; and to Miss E. W. M. Johnson for her help with the biochemical investigations.

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A CASE OF ACUTE MONONITROBENZENE POISONING

BY

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Mononitrobenzene, or oil of mirbane, is a yellow oily liquid which on account of its strong smell is also known as "artificial essence of bitter almonds." Since it was first prepared early in the nineteenth century many cases of poisoning with this substance have been recorded—by absorption through the skin, by inhalation, or when taken by mouth.

Poisoning by skin absorption has followed the use of soap scented with it (Nicholson, 1862), spilling the fluid on the clothes (Loeb, Bock, and Fitz, 1921; Hamilton, 1919–20; Letheby, 1863–4), or application to the hair of anti-louse preparations made with it (Wolpe, 1920; Bohland, 1919; Schultz, 1915). Shoe dyes often contain nitrobenzene as a solvent, and the wearing of recently dyed shoes before they are properly dry has led to many cases of poisoning. Muehlberger (1925) has reviewed the literature on this subject and pointed out that aniline is the solvent most commonly employed, and may give rise to similar symptoms. Levin (1931) has reported a case of orthotoluidine poisoning caused in the same way. Marking-ink also may be prepared with nitrobenzene or aniline, and babies seem to be very easily affected by newly marked napkins: Rayner (1886) first reported a series due to aniline, and Ewer (1920) and Thomsen (1921) have reported cases due to nitrobenzene. In many of these episodes inhalation may have contributed to the intoxication: acute poisoning due to inhalation alone is relatively infrequent, but Stevenson and Forbes (1942) and Stevens (1928) have reported cases following the use of nitrobenzene in bed-bug exterminators.

Poisoning by ingestion has occurred in numerous ways. The majority of cases are accidental, either errors in dispensing (Carter, 1936; Leader, 1932; Thomas, 1926) or mistakes by patients as reported by Chapman and Fox (1945), where furniture polish containing nitrobenzene was taken instead of an alkaline stomach mixture. Hogarth (1912) published a case following the rubbing of nitrobenzene on the gums as an anodyne for toothache. Other cases have arisen from taking alcoholic drinks which have been contaminated with the substance (Loeb, Bock, and Fitz, 1921; Scott and Hanzlik, 1920) or from drinking a nitrobenzene preparation when intoxicated (Adler, 1934; Wandel, 1919). Food contaminated with the liquid is a rare cause (Hilbert, 1915), though Taylor (1864) reported the case of a woman who tasted the flavouring she was going to use in some pastry and developed nitrobenzene poisoning. Curiosity on the part of children accounts for some cases (Nobécourt and Pichon, 1924); a few are suicidal (Fullerton, 1930; Schild, 1895); and on many occasions the liquid has been taken as an abortifacient, usually without success (Güntz, 1930; Schnopfhagen, 1927; Spinner, 1917; Schild, 1895).

Chronic poisoning is usually industrial. Workers in aniline plants may develop symptoms from nitrobenzene inhalation; it is less common than aniline intoxication, but is more dangerous when it does occur. Engel (1934), Balsac *et al.* (1930), Hamilton (1919–20, 1921), and Letheby (1863–4) have discussed industrial nitrobenzene poisoning, and Adams (1912) has described an unusual case of non-industrial chronic intoxication.

Case Report

The patient, a Polish girl aged 19, was admitted to University College Hospital on July 23, 1947. About three months previously, while she was in Germany as a displaced person, she had married an English soldier, who brought her to London and left her with her mother-in-law while he returned to his unit. She did not get on very well in her new home, and partly out of curiosity and partly, one suspected, hoping to get her husband repatriated she decided to taste the fluid in a bottle labelled "poison." This bottle had been bought by her late father-in-law many years previously and was lying about the house; her husband had warned her that it was poisonous and forbidden her ever to touch it. About 6.30 p.m. on July 22 she poured some of the fluid into a glass and sipped it; she felt nauseated, and vomited several times during the night. The next morning she was seen to be blue, and was therefore sent to hospital.

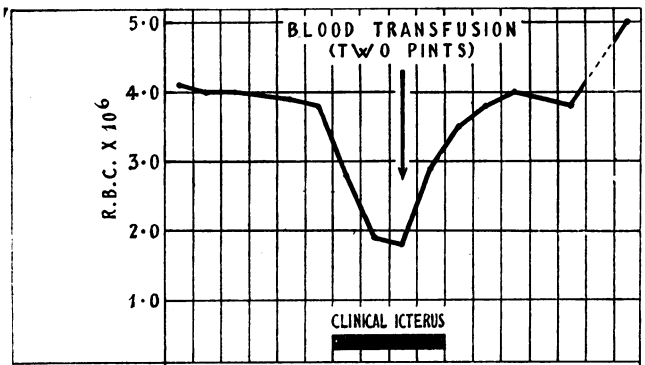
When seen at 3 p.m. on July 23 she was fully conscious and well orientated. She showed "blue-grey" cyanosis and was vomiting repeatedly, the vomit being bright yellow but without smell. She was afebrile; pulse rate 90; respiration was of normal depth and rate, but the breath smelt strongly of almond essence. Physical examination revealed no other abnormalities. The urine was dark in colour and became darker on standing; it contained a trace of albumin and did not reduce Benedict's reagent.

The stomach was washed out with saline, after which the vomiting ceased. Oxygen inhalations failed to affect the cyanosis, and blood withdrawn from a vein was brownish in colour and shown to contain methaemoglobin. 20 ml. of 0.5% solution of methylene blue was injected intravenously and within 30 minutes the patient's colour was restored to normal.

The next day (July 24) her breath still smelt of almond essence and continued to do so until July 27. The cyanosis was then nearly as deep as before the injection of methylene blue, but it did not seem to be inconveniencing the patient. Oral methylene blue, 2 gr. (130 mg.) four-hourly, was given for two days, and subsequently ascorbic acid, 100 mg. four-hourly, but neither of these seemed to accelerate the disappearance of the cyanosis, which ceased to be detectable on July 29. The urine on July 25 was of normal colour, but still contained a trace of albumin.

On July 29 it was observed that the patient was faintly icteric, and that a severe haemolytic anaemia was developing (see Chart). On July 30 and 31 she passed urine that was almost black, and spectroscopic examination showed that it contained haemoglobin and methylene blue; a sample of plasma on the latter date contained methaemalbumin and haemoglobin. Red cell fragility showed haemolysis starting at 0.48% saline and complete at 0.28%, and a blood film revealed very marked anisocytosis, polychromasia, punctate basophilia, and six

nucleated red cells per 100 white cells. By July 31 her blood pressure had fallen from its initial level of 110/85 to 98/50 and her pulse rate had risen to 104; it was therefore decided to give a transfusion of 2 pints (1.36 litres) of blood. Her condition subsequently improved rapidly, and she left hospital on Aug. 8. When seen on Aug. 25 she had no symptoms.



DATE	JULY 23	24	25	26	27	28	29	30	31	AUGUST 1	2	3	4	5	6	25
Hb% HALDANE	68	76	82		70	68	56	40	40	64	74	72	78		80	104
W.B.C.	15,000		9,800		12,000	15,000	17,000	17,700		5,400	7,400	4,400	6,800		6,500	10,000
VAN DEN BERGH						4u.					4u.					
RETICULOCYTES								11%	20%							

Chart showing haemolytic action of nitrobenzene.

The bottle from which the fluid was taken contained a yellow oily liquid smelling strongly of almond essence and rather indistinctly labelled "nitrobenzene." That the bottle contained nitrobenzene was subsequently confirmed chemically. It was impossible to ascertain the purpose for which it had originally been obtained.

Discussion

Nausea and vomiting are the first symptoms after the oral ingestion of nitrobenzene; they develop within a few minutes, and are followed in from one to twelve hours by the appearance of cyanosis and in severe cases by neurological symptoms. In cases of poisoning by skin absorption or inhalation the cyanosis develops more rapidly. It is now generally considered that the cyanosis is due to the development of methaemoglobin in the red blood cells, although many earlier investigators—for example, Loeb, Bock, and Fitz (1921)—were unable to detect methaemoglobin in the blood, and postulated the development of a nitrobenzene haemoglobin compound. Hamblin and Mangelsdorff (1938) devised a recording spectrophotometer and used this to detect methaemoglobin, which they found in the blood in all cases of nitrobenzene poisoning in amounts proportional to the clinical condition and cyanosis.

The neurological symptoms that may be seen in the early stages are progressive drowsiness leading to coma and in fatal cases respiratory paralysis. These have been attributed either to a direct toxic action of the poison on the central nervous system or to anoxaemia. Loeb, Bock, and Fitz (1921) reported the case of an unconscious patient with a blood-oxygen-carrying capacity of 6.2 volumes % who recovered consciousness on being given a blood transfusion: although cases have been reported showing spontaneous recovery from nitrobenzene coma (Güntz, 1930), it is suggestive that in this case recovery was due to improved oxygenation following the transfusion. Steele and Spink (1933) report a case of aniline poisoning with cyanosis and coma in which recovery of consciousness followed the intravenous administration of methylene blue, which converted the methaemoglobin to haemoglobin and restored the oxygen-carrying capacity of the blood. However, Levin (1927), in investigations of the effect of nitrobenzene on animals, found that, whereas dogs, cats, and rats developed cyanosis and neurological symptoms, rabbits and guinea-pigs failed to develop cyanosis but nevertheless died. It appears therefore that, although anoxaemia may play a part in the production of neurological symptoms and death, a direct toxic action on the nervous system is an important factor.

In all moderately severe cases of nitrobenzene poisoning some haemolysis is found, starting about the fifth or sixth day. Engel (1934) mentions that the haemoglobin level may fall to 30%; Leinoff (1936) records a case in which it was 45%. Clinical icterus is present when haemolysis is severe and the spleen occasionally becomes palpable (Hilbert, 1915; Schild, 1895). The process is usually self-limiting, and blood transfusion is not often required.

Late sequelae are unusual in cases of acute poisoning, although Adler (1934) reported a case in which a neurological disturbance suggesting a lesion of the basal ganglia followed four days' unconsciousness due to nitrobenzene; and Grafe and Homburger (1914) reported a case in which mental deterioration was a sequel. It is possible that in the first case prolonged cerebral anoxia was an important factor.

Laboratory Investigations

In the early stages spectroscopic examination of the blood is useful in confirming the presence of methaemoglobin. A daily red cell count is advisable to ascertain the severity of the haemolytic process. Haemoglobin estimations are satisfactory if done by the Sahli method, but in this case only that of Haldane was available, and although the results are recorded in the Chart the presence of methaemoglobin makes them unreliable. The white blood cells may show a polymorphonuclear leucocytosis in the early stages, and Loeb, Bock, and Fitz (1921) report 40,000 per c.mm. in one case; a second rise during the haemolytic phase may also be found.

The urine initially may be dark, especially on standing; this has been noted on many occasions, and, according to Loeb, Bock, and Fitz (1921) and to Meyer-München (1905), is due to nitrobenzene being excreted as para-amidophenol. It is often said that the urine may contain a reducing substance, but this is rarely reported in case summaries, although Wolpe (1920) stated that one of his patients had 0.1% sugar in the urine the day after poisoning (method of testing not mentioned). Engel (1934) attributes this property of the urine to the presence of glycuronic acid, with which para-amidophenol is conjugated for excretion. The passage of dark urine in the haemolytic phase is unusual, although Güntz (1930) mentions it in his case.

Treatment

The recognition of acute nitrobenzene poisoning should not be difficult with the extreme cyanosis and characteristic smell, and if the history suggests oral ingestion the stomach should be washed out. If the patient is unconscious, steps should be taken to restore the oxygen-carrying capacity of the blood, a procedure which may terminate the coma although it will not affect the direct toxic action on the nervous system. Blood transfusion and replacement transfusion have both been used with good results: Chapman and Fox (1945) had a patient in semicoma who was much improved by venesection and transfusion of 3 pints (1.7 litres) of blood. In view of the ability of methylene blue to convert methaemoglobin to haemoglobin, such measures would seem to be unnecessary, although in the case of replacement transfusion it has the theoretical advantage of reducing the amount of poison acting on the nervous system. Methylene blue was first advocated as a result of animal experiments for use in cyanide and carbon monoxide poisoning. In the latter it was considered to improve cell metabolism, whereas in the former it was thought to convert

haemoglobin to methaemoglobin, which fixed the cyanide and prevented its toxic action (Wendel, 1933). However, despite this evidence, Steele and Spink (1933) used methylene blue in two cases of aniline poisoning with dramatic disappearance of methaemoglobinaemia, and Williams and Challis (1933) in one case. Subsequently Wendel (1937) agreed that it had this action in man in the dose used; and Hartman, Perley, and Barnett (1938) made a detailed study of it as an antidote for methaemoglobinaemia following sulphonamide therapy. Only two reports have been found of its use in nitrobenzene poisoning: Walterskirchen (1939) employed an unstated amount of 1% solution of methylene blue intravenously, and the cyanosis cleared in 15 minutes; and Leinoff (1936) gave 50 ml. of a 1% solution intravenously, and describes the patient as at first becoming darker blue, then within one hour the condition improved and the finger-nails became pink. He does not mention a return of the cyanosis, but this is implied in the subsequent statement that it disappeared completely in a few days. The dose given in the case reported here is much smaller than that advised by Hartman *et al.* (1938)—1–1.5 mg. per kg. The subsequent oral administration had less effect than would have been expected in view of the finding of the same workers that 1–2 gr. (0.065–0.13 g.) four-hourly controlled sulphonamide cyanosis. The use of ascorbic acid was suggested by Deeny, Murdock, and Rogan (1943), who reported on its use in congenital methaemoglobinaemia, and by Carnrick, Polis, and Klein (1946) in the acquired type, although in this case it was really given too late to say whether it was beneficial.

There does not seem to be any danger in giving methylene blue in these doses, although coloration of the urine may surprise the patient and injection outside the vein may cause a severe and painful inflammatory reaction.

Subsequently the extent of the haemolytic process must be watched, and, if the haematological or clinical condition demands it, blood transfusion should be given. In the present case it is probable that the haemolysis was maximal at the time of the transfusion and that the condition would have improved satisfactorily without it.

Summary

A case of acute nitrobenzene poisoning following oral ingestion is reported. Cyanosis and haemolytic anaemia were the outstanding clinical features. Methylene blue was used in the treatment of the methaemoglobinaemia, and the haemolytic anaemia was so severe as to need a blood transfusion.

I have to thank Dr. F. M. R. Walshe for permission to publish this case, and Dr. M. Maizels, Dr. M. E. Morgans, Dr. E. Roderic-Evans, and Mrs. C. E. Work for the investigations.

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HETEROTOPIC OSSIFICATION OF AN APPENDICULAR MUCOCELE

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By the term "heterotopic ossification" is meant the appearance of osseous tissue in an organ which has no ontogenetic relationship to the process of ossification. The spontaneous occurrence of heterotopic ossification has been observed in the most unexpected tissues and organs, as, for example, aneurysmal walls, old haematomata, laparotomy scars, injured muscles and nerves (Leriche and Policard, 1926), arterial walls (Mönckeberg, 1902), tonsils (Reitmann, 1903), aortic valves (Rosenstein, 1900), the anterior chambers of the eyes (Koch *et al.*, 1939), tissues affected by elephantiasis (Kleine, 1929), and of course tumours (Leriche and Policard, 1926; Törö, 1935).

Experimentally, the condition has been obtained by ligation of the renal vessels, in granulation tissue by a variety of methods (Leriche and Policard, 1926), by grafting a portion of gall-bladder mucosa, urinary-bladder mucosa, or even gastric mucosa into various connective tissues (Cavalli, 1939; Jung and Cemil, 1935; Leriche and Lucinesco, 1935; Lucinesco and Cavalli, 1935, 1936; Santa and Marcacci, 1938), or when a portion of an aponeurosis has been used to replace a defect in the urinary bladder wall (Neuhof, 1918-20; Huggins, 1931; Phemister; Copher and Key).

The mechanism of heterotopic ossification is still a matter of controversy. Conheim supported the theory of latent embryonic points of ossification; Ollier that of periosteal displacements; Busch, Macewen, and Ribbert that of the haematogenous seeding of osteoblasts. At present the hypothesis of Leriche and Policard is favoured —namely, that the principal requirements for the occurrence